Seminar

# Human T-lymphotropic virus type I infection

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**Human T-cell lymphotropic virus type I (HTLV-I) is the first human retrovirus to be associated with malignant disease—namely, adult T-cell leukaemia/lymphoma. HTLV-I has also been associated with several non-malignant conditions, notably the chronic neurodegenerative disorder, HTLV-I associated myelopathy (also known as tropical spastic paraparesis), infective dermatitis of children and uveitis. More recent evidence points to disease associations not previously linked to HTLV-I. Thus, the disease spectrum of HTLV-I is not fully known. HTLV-I has a worldwide distribution with major endemic foci in the Caribbean and southern Japan. The public health importance is confirmed by the major routes of transmission, which are mother-to-child, blood transfusion, and sexual activity. Unfortunately, no vaccine is available yet and there is no proven treatment for advanced HTLV-I disease.**

Human T-cell lymphotropic virus type I (HTLV-I) is the first human retrovirus associated with a malignancy. In 1980, the virus was isolated from cell lines derived from patients diagnosed with cutaneous T-cell lymphoma in the United States.[1,2] These patients really had adult T-cell leukaemia/lymphoma (ATL), a distinct T-cell lymphoid malignancy described in Japan in 1977.[3,4] A viral aetiology and genetic susceptibility were hypothesised as causative factors. Subsequent seroepidemiological and molecular evidence revealed that retroviruses isolated from patients in the USA and Japan were identical and that this was the putative aetiological agent of ATL.[5,6] We now know that HTLV-I infection has a much broader spectrum of disease manifestations, including HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP),[7,8] uveitis,[9] and an infective dermatitis of children.[10] Several inflammatory and immune-mediated conditions such as polymyositis, arthropathy, Sjögren's syndrome, and facial nerve palsy have been associated with HTLV-I, although a clear aetiological relationship has not been established.[11–13] Here we focus on the epidemiological, clinical, and biological features associated with HTLV-I disease.

## Virology

HTLV-I is an enveloped, double-stranded RNA, type C virus (Retroviridae family, subfamily oncovirus).[14] It is T-cell tropic, causes T-cell proliferation, and has a propensity to establish persistent infection. Transmission of HTLV-I is highly cell-associated. The receptor(s) for entry of HTLV-I into the host's cell are unknown. Once inside it synthesises copies of DNA by reverse transcriptase and integrates into the host's genome as provirus. The HTLV-I genome (figure 1) contains three structural genes *gag*, *pol*, and *env*, two principal regulatory genes (*tax* and *rex*), and the long terminal repeats (LTRs).[14,15] HTLV-I can transform and immortalise cells in vitro. Despite its oncogenic properties, the virus does not possess cell-derived oncogenes as other type-C transforming retroviruses do. The *gag* gene encodes core proteins p19 and p24, *pol* encodes RNA-dependent DNA polymerase (reverse transcriptase), and *env* encodes the small transmembrane (gp21) and large external envelope (gp46) glycoproteins. The HTLV-I protease has as its primary role the processing of the *gag* gene products. The *tax* and *rex* regulatory genes transactivate viral replication and regulate expression of viral proteins. The *tax* protein is responsible for activation of the LTRs. The U3 region of the LTRs primarily controls transcription of the provirus.

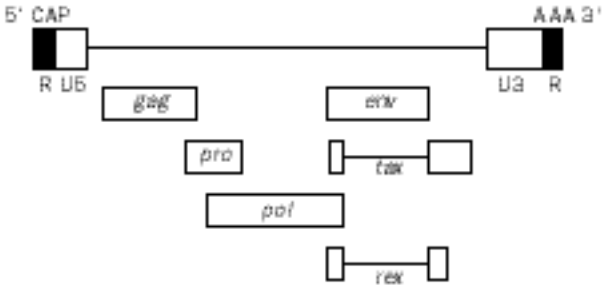


Figure 1: **Structure of HTLV-I genome**
Major coding domains include structural genes *gag, pro* (protease), *pol* (reverse transcriptase), and *env*. Regulatory genes *tax* and *rex* are encoded in regions joined by RNA splicing (horizontal line). These genes are flanked by two long-terminal repeat sequences (LTRs). Terminal noncoding sequences include two direct repeats (R) and a U5 (5' unique) and U3 (3' unique) sequence. Redrawn with permission, from figure 2B in Retroviruses (Coffin JM, Hughes SH, Varmus HE, eds, published by Cold Spring Harbor Laboratory Press).

## Methods of detection

When infection is established, antibodies to core, envelope, and *tax* proteins appear in serum. In the first 2 months after primary HTLV-I infection, antibody to *gag* proteins predominates with anti-p24 appearing before anti-p19. Antibody to recombinant gp21 is the earliest appearing envelope reactivity with native anti-gp46 appearing later. Anti-*tax* appears much later.[16]

Enzyme-linked immunoabsorbent assays (ELISA) using disrupted whole-virus lysate are the most commonly used screening assays for human sera or plasma in the USA and Europe. A modified assay is also available with recombinant antigens or peptides to enhance sensitivity.

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In Japan, the particle agglutination assay is most commonly used for screening. Guidelines from the US Public Health Service, WHO and other international groups,[17] recommend that newly identified seropositive individuals have additional blood collected for repeat testing to eliminate possible technical errors. Repeatedly reactive samples require confirmation with a recombinant western blot (WB) assay. Confirmatory criteria require WB reactivity to *gag* (p19 or p24) and *env* (gp21 or pg46) gene products (figure 2). The most commonly used WB assays are constructed from whole-virus lysate with the addition of recombinant envelope antigens (rgp21) and/or HTLV-I (rgp46I) and HTLV-II (rgp46II) specific envelope peptides to distinguish HTLV-I from HTLV type II. HTLV-II shares 60% genomic homology with HTLV-I,[15] and it is difficult to distinguish the two unless virus-specific reagents are used. This distinction is important because HTLV-II is less pathogenic than HTLV-I.[18] The polymerase chain reaction (PCR) can also be used on peripheral blood mononuclear cells from infected individuals to distinguish HTLV-I from HTLV-II and to detect DNA in tumour tissue and other biological specimens.[19]

## Epidemiology

### *Geographical distribution*

Foci of HTLV-I infection are found in geographical clusters, affecting several million individuals worldwide.[20] The infection is endemic in southern Japan, the Caribbean, parts of Africa, the Middle East, South America, the Pacific Melanesian islands, and Papua New Guinea. HTLV-I carriers have been identified among immigrants from endemic areas residing in the USA and Europe.

Population-based studies have shown that HTLV-I seroprevalence ranges from 3–6% in Trinidad, Jamaica, and other Caribbean islands[21,22] to 30% in rural Miyazaki, southern Japan.[23] The seroprevalence among low-risk populations in the USA and Europe is less than 1%. The dynamics of infection are influenced by changes in environment. For example, seroprevalence declines over successive generations in families who have migrated from endemic to non-endemic areas.[24] Changes in behaviour and lifestyle such as marriage outside the migrant community and improved living conditions may explain this decline.

Population HTLV-I seroprevalence increases with age and is twice as high in females.[22] In Jamaica 9·1% of men over 70 and 17·4% of women over 70 were seropositive. In Japan, HTLV-I seroprevalence in persons over 80 was 50% in females and 30% in males.[23] This gender difference usually emerges after 30 years of age and probably reflects more efficient transmission of the virus from males to females in the sexually active years.

### *Modes of transmission*

Transfusion is perhaps the most efficient mode of virus transmission; the probability of seroconversion in a recipient of contaminated blood is 40–60%[25,26] and the median time to seroconversion is an estimated 51 days.[26] Thus, screening of blood donors to prevent the introduction of new infection is as important in areas of low endemicity as in highly endemic areas. Southern Japan was among the first areas to screen blood; the USA followed in December, 1988.

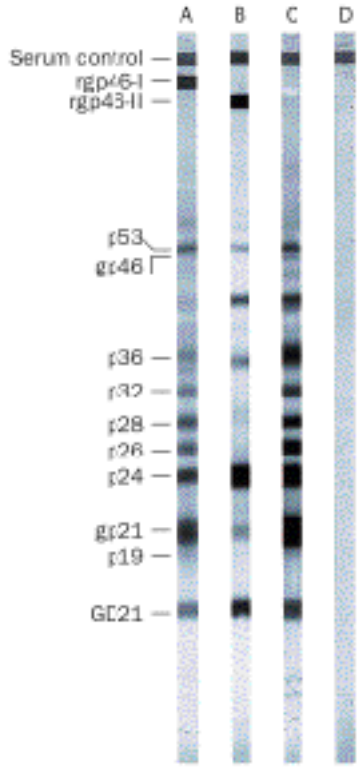


Figure 2: **Confirmatory western blotting**
(A)=HTLV-I seropositive ATL; (B)=HTLV-II seropositive, (C)=HTLV seropositive with undefined subtype in ATL, subtype determined as HTLV-I by PCR DNA typing; (D)=negative. Seropositivity is indicated by band reactivities to *gag* (p24 or p19) and *env* (GD21); additional *env* reactivity to rgp46I and rgp46II required to distinguish HTLV-I from HTLV-II. An "indeterminate" western blot has specific bands but does not meet criteria for seropositivity. A negative blot has no reactivity to HTLV specific band reactivity. (Genelabs Diagnostics [Pte] Ltd, Singapore.)

Of paramount concern was the need to prevent transfusion-acquired HAM/TSP, especially following reports of cases developing only weeks to months after transfusion of infected blood components.[27] Packed red blood cells, whole blood, and platelets but not fresh frozen plasma were the source of virus transmission, suggesting that white blood cells were the reservoir. The fact that units stored for more than 7 days were less likely to transmit the virus supported this theory. Host-related factors such as preexisting immunosuppression at time of transfusion were also important risk factors.[26] Although very rare, development of ATL as a second malignancy after transfusion of infected units to patients with haematological malignancies has been reported.[28] Fortunately screening can eliminate infected units from the donor pool.[29] As more data become available on the impact of HTLV-I, country-specific decisions are being made on the costs and benefits of blood donor screening for HTLV-I. However, most HTLV-I infections are attributable to transmission from mother to child through prolonged breastfeeding or by sexual contact later in life.

Mother-to-child transmission was postulated early in the investigation of ATL because of clustering of HTLV-I infection in mothers and their offspring.[30] The observation that HTLV-I could be transmitted by breast milk in a marmoset model drew attention to this as a possible mechanism in mother-to-child transmission in humans, and later this was confirmed by prospective studies in Japan and Jamaica.[31,32] The probability of mother-to-infant transmission is 18–30%. Maternal factors, including

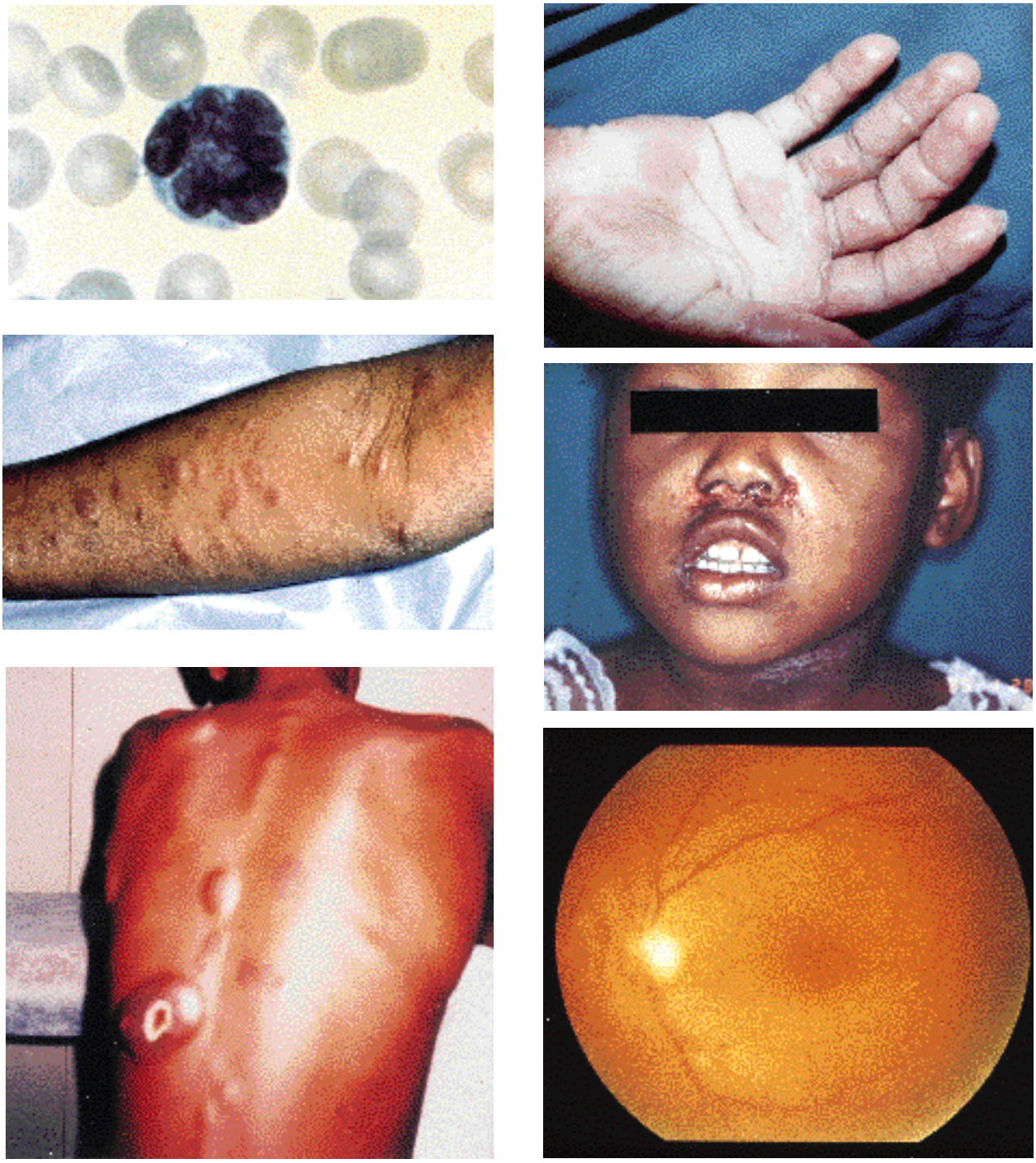

Figure 3: **Microscopic and clinical features associated with HTLV-I related disease**
Top left: Abnormal lymphocyte (flower cell) in ATL.
Top right, middle left, bottom left: Skin lesions associated with ATL (plaques, nodules, and ulcers).
Middle right: Infective dermatitis with nasal discharge and crusting of anterior nares; eczema of neck and external ear.
Bottom right: Ophthalmoscopy at acute stage of HTLV-I uveitis, showing pale optic nerve, mild vasodilation (retinal vasculitis) and moderate vitreous opacities (vitreitis).

higher HTLV-I antibody titre, prolonged ruptured membranes during delivery, and low socioeconomic status are risk factors.[32] Breastfeeding for more than 6 months has been associated with transmission, which has led to the hypothesis that shortening the duration of breast feeding may reduce the risk of HTLV-I transmission. However, intervention studies in Japan have found that infection still occurs in about 3% of children who were not breast-fed.[30] Thus, other methods besides curtailment of breast feeding may be required to interrupt transmission completely. In primate models, prophylactic virus-specific immunoglobulin prevents infection.[33] A combination of artificial feeding, prophylactic immunoglobulin, and perhaps antiretroviral therapy may be useful in further reduction of mother-to-child transmission. Some investigators are also exploring the feasibility of an HTLV-I vaccine.[34]

Sexual transmission has the potential to introduce infection into previously unexposed groups, but it has

been difficult to define precisely the actual impact of transmission by this route. HTLV-I is transmitted four times more effectively from males to females than the reverse[35] at a rate of 4·9 per 100 person-years among females married to an infected male compared with 1·2 among males married to an infected female.[36] The transmission risk to females is greater if the partner has high antibody titres or antibody to *tax* proteins. The risk of female-to-male transmission appears to be associated with penile sores/ulcers and diagnosis of syphilis among males.[37]

## HTLV-I associated diseases

### *Adult T-cell leukaemia/lymphoma*

ATL is a mature T-cell non-Hodgkin lymphoma with a leukaemic phase characterised by circulating, activated CD4+/CD25+ T-cells.[4] HTLV-I provirus is randomly integrated into the host genome of malignant cells and tumour tissue in all ATL patients.[38] Often the genome is partly deleted, resulting in defective virus which may provide a mechanism for escape from immune surveillance.[39] *tax* regulatory protein is thought to play an important part in malignant transformation and lymphomagenesis[15] but the exact mechanisms remain elusive. Infection early in life is crucial in the development of ATL.[40] The disease develops after a long incubation period, with an estimated lifetime risk of about 5% in individuals infected before the age of 20 years.[41] The incidence rate is 2–4 per 100 000 person-years[41,42] with a higher risk in males than in females. The average age of onset is 60 years in Japan but only 40 in Jamaica, Trinidad, and Brazil.[41,43] This difference is unexplained, although variation in seroprevalence by age, host and environmental factors contributing to longer life expectancy may have a role.

Diagnostic criteria for ATL include seropositivity for HTLV-I, morphologically unique abnormal lymphocytes with cleaved, convoluted nuclei ("flower cells") (figure 3), histology and/or cytology of malignant cells with T-cell immunophenotype, and serum lactate dehydrogenase activity.[44] The disease is classified on clinical and laboratory criteria as acute ATL, chronic ATL, lymphoma, or smouldering ATL but the distribution of these subtypes varies geographically. In Japan, 57% of early cases are acute ATL, 19% chronic, 19% lymphoma, and 5% smouldering subtype.[44] In Jamaica, the proportion is slightly higher for lymphoma subtype (27%) and lower for acute (47%) with a similar frequency for chronic (21%) and smouldering (5%) subtypes.[45] 40% of cases have widespread or localised skin lesions at diagnosis (figure 3). Large nodules, plaques, ulcers, and a generalised papular rash are common lesions, and may appear on the limbs, trunk, or face. Lymphadenopathy, hepatosplenomegaly, and hypercalcaemia are also common. Immunosuppression is well documented, manifesting as bacterial and opportunistic infections which contribute to a poor prognosis. The most common opportunistic infections are *Pneumocystis carinii* pneumonia, serious fungal infections, and strongyloidiasis.[46]

Standard chemotherapy for non-Hodgkin lymphoma is ineffective in ATL. The median survival for acute and lymphoma subtypes is less than a year; patients with chronic and smouldering ATL may survive longer. A combination of interferon-α and zidovudine has been found effective,[47,48] but less so in previously treated patients.[49] No randomised trials comparing this regimen with standard therapy for non-Hodgkin lymphoma have been done.

### *HAM/TSP*

The cause of TSP was unknown for a long time after the first case was described in 1956 in the Caribbean.[50] Thirty years later HTLV-I antibodies were found in the serum and cerebrospinal fluid of patients with progressive neurological disease, indicating that HTLV-I was also neurotropic.[7] The disease was designated HAM in Japan,[8] and in 1988 a WHO group decided that the two diseases are the same.[51] Clinical features of HAM/TSP include muscle weakness in the legs, hyperreflexia, clonus, extensor plantar responses, sensory disturbances, urinary incontinence, impotence, and low back pain. Laboratory diagnosis includes presence of the virus and its antibodies in cerebrospinal fluid, brain and spinal cord tissues. Magnetic resonance imaging of the spinal cord may reveal atrophy, usually localised to the thoracic region, while imaging of the brain shows subcortical and periventricular white-matter lesions. These findings tend to correlate with age greater than 50, and older patients tend to progress faster to paralysis. The average age of diagnosis is 40 which is commonly preceded by adult acquired infection. The lifetime risk among HTLV-I carriers is estimated to be less than 2%,[53] lower than that of ATL. The age-standardised incidence in major endemic areas is about 2 per 100 000 person-years.[53] In contrast to ATL, HAM/TSP is more common in women than men at all ages.

It is unclear why some HTLV-I carriers develop disease while others do not; nor do we know why ATL develops in some and HAM/TSP in others. Because ATL and HAM/TSP rarely coincide,[54] a differential immune response to infection, as reflected by specific host genetic factors such as human leucocyte antigens (HLA), may be the explanation.[55] Three mechanisms have been proposed to explain the role of HTLV-I in the development of HAM/TSP.[56] In the first model the neurological damage is a direct consequence of persistent CNS infection, resulting in chronic activation and destruction of tissue by a cellular immune attack. HTLV-I specific CD8+ cytotoxic T lymphocytes (CTLs) may have an important role in this scenario.[57] CTL counts are high in peripheral blood lymphocytes and CSF of HAM/TSP patients. CTLs have also been identified in the spinal cords of HAM/TSP patients and increase in numbers as disease progresses. The CTL target is thought to be glial in origin and the mechanism involved could be glial lysis or cytokine release. A second theory implicates autoimmunity; HTLV-I infection promotes activation of autoreactive T lymphocytes which migrate to the CNS and recognise target antigens in the CNS. These autoreactive cells may secrete cytokines and result in CNS inflammation and tissue damage. A third idea is that HTLV-I infected CD4+ T cells enter the CNS and immunocompetent cells responding to HTLV-I antigens produce cytokines or result in damage of bystander glial cells.

HAM/TSP is a progressively disabling disorder and its secondary complications may lead to death after many years. Early disease can be tempered with systemic or intrathecal corticosteroids but no treatment for chronic, advanced disease has been found. A few patients have had

**Criteria for diagnosis of infective dermatitis**

**Major criteria ***

(1) Eczema of scalp, axillae, and groin, external ear and retroauricular areas, eyelid margins, paranasal skin, and/or neck
(2) Chronic watery nasal discharge without other signs of rhinitis and/or crusting of anterior nares
(3) Chronic relapsing dermatitis with prompt response to (but prompt recurrence on withdrawal of) antibiotics
(4) Usual onset in early childhood
(5) HTLV-I seropositivity

**Minor or less specific criteria**

Positive cultures for *S aureus* and/or β-haemolytic streptococci from skin or anterior nares
Generalised fine papular rash (in most severe cases)
Generalised lymphadenopathy with dermatopathic lymphadenitis
Anaemia
Raised erythrocyte sedimentation rate
Hyperimmunoglobulinaemia (IgD and IgE)
Raised CD4 count, CD8 count, and CD4/CD8 ratio

*Four major criteria required for diagnosis, with mandatory inclusion of 1, 2, and 5; to meet criterion 1, at least two of the sites must be affected.[62]

temporary relief of symptoms from zidovudine, danazol, and vitamin C[58–60] but no randomised trials have been done.

*HTLV-I associated infective dermatitis*

Infective dermatitis was first reported as a unique clinical entity in Jamaican children in 1966.[61] In 1990 its association with HTLV-I was discovered.[10] Infective dermatitis has been reported from several HTLV-I endemic populations, including Japan, Trinidad, Brazil, and Colombia. The clinical and laboratory criteria of ID are summarised in the panel.[62] The disease is characterised by a severe exudative dermatitis of the scalp, external ear and retroauricular areas, eyelid margins, paranasal skin, neck, axillae, and groins as well as a generalised fine papular rash (figure 3). There is also a chronic watery nasal discharge sometimes associated with crusting. *Staphylococcus aureus* and/or β-haemolytic streptococci are commonly cultured from the anterior nares and skin. The disease responds to antibiotics, but relapses if antibiotics are withdrawn. The average age of disease onset is 2 years and 60% of patients are female. The incidence and prevalence of disease are undefined, as is the pathogenesis. Microscopy reveals an inflammatory lymphocytic infiltrate within the skin lesions, suggesting a strong antiviral host response. The skin manifestations usually become less severe with age perhaps with maturation of the immune system. Epidemiological data suggest that infective dermatitis is a harbinger of later development of ATL or HAM/TSP.[63] Familial clustering suggests that host genetic and environmental interaction may be an important determinant of subsequent disease outcomes.[64]

*HTLV-I associated uveitis*

Uveitis is an intraocular inflammatory disorder associated with infectious causes including tuberculosis, syphilis, toxoplasmosis, and cytomegalovirus or non-infectious causes (Behçet's syndrome, sarcoidosis, and Vogt-Koyanagi-Harada syndrome). A firm cause is not identified in about 40% of cases. Unexplained (idiopathic) uveitis was observed to be very common in the HTLV-I endemic areas of Kyushu, Japan, leading to speculation that HTLV-I infection might be the cause.[9,65] 35% of patients with idiopathic uveitis were found to be HTLV-I seropositive compared with 10% of uveitis cases where another cause had been identified. A patient with HTLV-I associated uveitis will often complain of blurred or foggy vision and acute, sudden onset of "floaters". Clinical examination reveals iritis (97%), vitreous opacity (92%), retinal vasculitis (62%), and retinal exudates and haemorrhages (20%) (figure 3). Unilateral disease is more common than bilateral (60% *vs* 40%). Most patients are below 50 years of age, including children,[66] and there is a slight female predominance (60%). Comorbid conditions include HAM/TSP and Graves' disease. The diagnosis requires ophthalmological and systemic evaluation to eliminate other possible causes of uveitis. Proviral DNA can be detected by PCR in mononuclear cells in peripheral blood and vitreous humor.[67] Both direct effects and autoimmune reactions mediated by these infected cells have been proposed as possible pathogenic mechanisms. The infiltrating cells in the eye express the inflammatory cytokine interleukin-6,[68] which may be responsible for the uveitis. Topical and systemic corticosteroids improve visual acuity.

*Wider spectrum?*

HTLV-I is thus the causative agent in clinical disorders affecting several organ systems. Excess morbidity and mortality due to causes not commonly associated with this retrovirus have recently been reported among carriers,[69] indicating that the full public-health impact of HTLV-I may be much greater than generally perceived.

## Clinical and biological markers of disease

One remaining challenge is our inability to determine risk factors for HTLV-I disease. Age at infection, routes of infection, and host and environmental factors seem to be important determinants but this information is usually not available. However, several factors may be useful in monitoring carriers. Infective dermatitis during early childhood and non-specific skin lesions in adulthood have been reported before the onset of ATL and HAM/TSP and may be a useful marker of subsequent disease. Uveitis in young persons may be an early sign of HTLV-I sequelae such as HAM/TSP. Increased numbers of abnormal lymphocytes and opportunistic infections are thought to presage development of ATL.[70] However, abnormal lymphocytes are non-specific; counts fluctuate over time, and these lymphocytes can disappear spontaneously or be detected in HAM/TSP patients without signs of malignancy.[51] Mononuclear or polyclonal expansion of HTLV-I infected cells in carriers, detected by PCR on the HTLV-I proviral genome, may also be useful.[71] However, clonality is not specific to cancer and may not be enough to identify risk for ATL and HAM/TSP.

Other viral markers have been studied. Quantitative PCR to detect proviral DNA seems to differentiate the various disease states and characterise risk of virus transmission.[72] In a prospective study of carriers, HTLV-I antibody titres strongly predicted ATL.[73] A strong, positive correlation between antibody titres and proviral DNA among asymptomatic carriers[72] suggests that proviral DNA load is likely to be high among carriers at high risk of ATL. Similarly, patients with HAM/TSP and uveitis are thought to have high antibody titre and proviral DNA levels.[67]

The level of *tax* mRNA and *tax* antibody may indicate the risk of ATL because concentrations of these markers are lower among ATL patients than in carriers.[74] *tax* is a target for HTLV-I specific CD8+ CTL immunity but since malignant ATL cells do not express *tax*, they are likely to escape cell lysis mediated by CTL. Alternatively, the lack of *tax* mRNA expression may result in a low CTL response. HAM/TSP patients have a vigorous CD8+ CTL response specific for HTLV-I *tax*.[57] The high levels of circulating CD8+ CTLs have an important role in disease pathogenesis probably through the promotion of inflammatory cytokine production.[75]

Because the level of CTL response against HTLV-I may be determined by HLA polymorphisms[55] the role of HLA in host susceptibility to infection and disease has been investigated. Japanese ATL patients have an increased frequencies in HLA class I and II (A26, B61 and DR9) compared with HTLV-I carriers.[55] However, in populations of African descent the HLA class I antigens significantly associated with ATL were different (A36, B18).[76] On the other hand, several class II alleles DRB1*1501 and DQB1*0602 distinguished ATL cases and carriers from healthy controls and HAM/TSP patients. These data suggested that specific alleles determine risk of infection and may be important in progression to ATL. Similar patterns of association were observed in both Japanese and Caribbean black populations.[77] Further studies of the role of HLA and other genes in host susceptibility to HTLV-I infection and related diseases are required.

## Vaccine prospects

Counselling infected individuals on sexual and breast feeding practices[78] is the only proven method to reduce HTLV-I related disease. However, the feasibility of vaccines to prevent infection or for treatment is being explored.[79] Preventive immunisation would be targeted towards populations at risk for the major transmission routes (ie, mother to infant and sexually acquired infection) while a therapeutic vaccine would be useful especially for carriers at high risk for disease with high HTLV-I proviral DNA and antibody levels. The genomic stability of HTLV-I and minimal strain variation between isolates are encouraging, as is the success of similar vaccines against bovine and feline leukaemia retroviruses.[80]

Animal models point to the characteristics of a successful vaccine.[80] Candidate vaccines should elicit an immunogenic response to *env* proteins, which are critical for infectivity, and a target for the induction of neutralising antibodies, and *gag* proteins, which stimulate cell-mediated immunity. The full spectrum of important immune responses remains to be defined. Synthetic peptides and recombinant proteins are being used to characterise immunodominant epitopes of HTLV-I.[81] These strategies should provide a useful synthetic vaccine based on structurally defined criteria designed to overcome individual major histocompatibility restriction. The ideal vaccine will be an oral one and one that is affordable for developing countries. However, additional investigations are needed to define a universally immunogenic vaccine using animal models.[82]

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